



# PEC UPDATE

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April Showers.....



Bring May  
Flowers!

## New Bioequivalency Subcategories for Approved Drug Products

Pharmacists have often used the Food and Drug Administration's (FDA's) *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the "Orange Book," for guidance in determining which products are therapeutically equivalent for generic substitution. The FDA recently established a new therapeutic equivalence evaluations code in the Orange Book that has caused some confusion.

The Orange Book refers only to products with the same active ingredients when defining therapeutic equivalence. This definition does not encompass different drugs in the same therapeutic category that are basically equivalent in therapeutic effect and can be used for the same condition (e.g., nonsteroidal anti-inflammatory drugs). These types of agents are better described as therapeutic alternates.

The FDA uses the following criteria to determine whether products are therapeutically equivalent:

1. They are approved as both safe and effective.
2. They are pharmaceutical equivalents; they contain identical amounts of the same active ingredient in the same dosage form and route of administration, and meet compendial standards of strength, quality, purity, and identity.
3. They are bioequivalent; (a) they do not present a known or potential problem, and they meet an acceptable in vitro standard, or (b) if they do present a potential problem, they are shown to meet an appropriate bioequivalence standard.
4. They are adequately labeled.
5. They are manufactured in compliance with the FDA's Good Manufacturing Practices regulations.

In order for drug products to be therapeutically equivalent, they must be pharmaceutically equivalent and bioequivalent. The FDA may consider products to be therapeutically equivalent even though they may have different shapes, packaging, flavors, preservatives, and expiration dates.

To help pharmacists determine which generic products are therapeutically equivalent to a reference drug product (i.e., typically the innovator drug or brand name product), a two-letter coding system is used in the Orange Book (see Table on page 3). The *first letter* informs the user whether two pharmaceutically equivalent products are therapeutically equivalent. Products designated as “A” drug products are considered by the FDA to be therapeutically equivalent and may be interchanged. Products designated “B” drug products are considered not therapeutically equivalent and should not be interchanged. The second letter of the code provides additional information about the FDA's evaluation.

The most common code in the “A” rated category is the “AB” rating, indicating that the product meets the necessary bioequivalence requirements. The FDA recently added subcategories to further define drug products within this category. In situations when more than one reference drug of the same strength has been designated under the same heading, a number is added to the end of the AB code to make a three character code, designated as AB1, AB2, AB3, etc. Three character codes for reference products and the corresponding generic product will be the same.

One example of this new coding system in the Orange Book is the evaluation of transdermal nitroglycerin patches. As an AB1 product, Nitro-Dur<sup>®</sup> Transdermal Infusion Systems (Key Pharmaceuticals) has been designated as the reference product with Minitran<sup>™</sup> Transdermal Delivery System (3M Pharmaceuticals) as the AB1 rated generic. Similarly, Transderm-Nitro<sup>®</sup> Transdermal Therapeutic System (Summit Pharmaceuticals) has been designated as the AB2 reference product with Nitroglycerin Transdermal System patch (Mylan Pharmaceuticals) designated as the AB2 rated generic.

Drugs coded with a three character code under a heading are considered therapeutically equivalent

only to other drugs with the same three character code under that heading. Thus, in the example of the nitroglycerin patches, the reference drug products (Nitro-Dur and Transderm-Nitro) are **not** therapeutically equivalent or bioequivalent to each other. Additionally, Minitran and the Mylan patch are **not** considered to be therapeutically equivalent or bioequivalent to each other, even though they both have an AB rating. Based on this new rating system, Minitran is only therapeutically equivalent to Nitro-Dur, and Mylan's nitroglycerin patch is only therapeutically equivalent to Transderm-Nitro.

These subcategories in the AB rating system will increase in number as bioequivalent generic products become available in categories where more than one reference drug product is listed. As these subcategories of AB1, AB2, etc. become more prevalent within the Orange Book, some of the confusion should subside. Pharmacists should be aware of the meaning of these subcategories when issues arise regarding drug product selection and generic substitution.

For additional information about the Orange Book and the information that it provides, readers are referred to the FDA's Home Page on the Internet at: <<http://www.fda.gov/cder/da>>. Additionally, PEC Update 94-06, 13 May 1994, contains a synopsis of the information available in the Orange Book. The PEC Update is available on the Internet at: <<http://www.ha.osd.mil/hppec2.html#Start>>. The Orange Book is available for purchase from the Government Printing Office. It is also available in Volume III of the USP-DI, published by the United States Pharmacopeial Convention.

***Adapted from:***

Anonymous. FDA develops new bioequivalency subcategories for “AB” rating. *Louisiana Board of Pharmacy Newsletter*. 1997;18(3):3.

Food and Drug Administration. Therapeutic Equivalence Evaluations Codes. In: *Approved Drug Products with Therapeutic Equivalence Evaluations*. Posted 15 Nov 1996. Available from: URL: <http://www.fda.gov/cder/da/adptheval.htm>

**Table.—Therapeutic Equivalence Evaluations Codes**

<b>"A" Drug Products</b>	
Drug products that the FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products. The two categories of "A" rated products include:	
1.	No known or suspected bioequivalence problems.
AA	Products in conventional dosage forms (capsules, tablets, liquids) not presenting bioequivalence problems
AN	Solutions and powders for aerosolization
AO	Injectable oil solutions
AP	Injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions
AT	Topical products
2.	Actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro tests supporting bioequivalence. These products are coded as <b>AB</b> .
<b>"B" Drug Products</b>	
Drug products that the FDA considers not to be therapeutically equivalent to other pharmaceutically equivalent products at this time. Actual or potential bioequivalence problems have not been resolved with adequate evidence of bioequivalence. Often the problem is with specific dosage forms rather than active ingredients.	
BC	Extended-release dosage forms (tablets, capsules, injections)
BD	Active ingredients and dosage forms with documented bioequivalence problems
BE	Delayed-release oral dosage forms (e.g., enteric-coated particles)
BN	Products in aerosol-nebulizer drug delivery systems
BP	Active ingredients and dosage forms with potential bioequivalence problems (e.g., injectable suspensions)
BR	Suppositories or enemas that deliver drugs for systemic absorption
BS	Products having drug standard deficiencies
BT	Topical products with bioequivalence issues
BX	Drug products for which the data are insufficient to determine therapeutic equivalence
B*	Drug products requiring further FDA investigation and review to determine therapeutic equivalence

## In the Literature..... Clinical Guidelines

The following clinical guidelines are listed for information purposes only.

### Agency for Health Care Policy and Research

Costa PT, Williams TF, Somerfield M, et al. Recognition and initial assessment of Alzheimer's disease and related dementias. *Clinical Practice Guideline No. 19*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 97-0702. November 1996.

Costa PT, Williams TF, Somerfield M, et al. Early identification of Alzheimer's disease and related dementias. *Clinical Practice Guideline, Quick*

*Reference Guide for Clinicians, No. 19*. AHCPR Publication No. 97-0703. November 1996.

Costa PT, Williams TF, Somerfield M, et al. Early Alzheimer's disease. *Patient and Family Guide, Consumer Guide No. 19*. AHCPR Publication No. 97-0704. October 1996.

These and other AHCPR Guidelines are available by writing or calling:

AHCPR Publications Clearinghouse  
P.O. Box 8547  
Silver Spring, MD 20907  
1-800-358-9295

Additionally, the full text of guideline documents for online retrieval is available on the Internet at: <http://www.ahcpr.gov/guide/> and selecting "Clinical Practice Guidelines Online."

### **New Asthma Guidelines Under Review by PEC**

The National Asthma Education and Prevention Program has recently released *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma*. The Pharmacoeconomic Center (PEC) is currently reviewing this new guideline report to determine if any changes to the Tri-Service Formulary (TSF) are necessary at this time. The PEC published its recommendations for asthma management in PEC Update 96-11, 16 August 1996.

The new asthma guidelines are available on the Internet from the National Heart, Lung, and Blood Institute at: < <http://www.nhlbi.nih.gov/nhlbi/lung/asthma/prof/asthmc.htm> >

### **Medical Journals on the World Wide Web**

Various medical journals have established World Wide Web sites for readers to access publications electronically. These journal Web sites vary in their content and organization. Most of the journals provide a table of contents listing for current and past issues. Some journals provide abstracts and selected full text of articles. Search capabilities are available for some journals as well. At this time the electronic version of most journals is available at no charge, although a few of the journals require on-line registration (no charge) to view current or past issue contents.

The following list of journals and Web addresses are examples of some of the journals available on-line through the Web that readers may find useful.

#### American Academy of Family Physicians

< <http://www.aafp.org/> > to access the following journals:

- *American Family Physician*
- *Family Practice Management*

#### American Academy of Pediatrics

< <http://www.pediatrics.org/> > to access the following journals:

- *Pediatrics*
- *PEDIATRICS electronic pages*

#### American College of Physicians

< <http://www.acponline.org/> > to access the following journals:

- *Annals of Internal Medicine*
- *ACP Journal Club*

#### American College of Rheumatology

< <http://www.rheumatology.org/frames.htm> > to access the following journals:

- *Arthritis & Rheumatism*
- *Arthritis Care & Research*

#### American Heart Association

< <http://www.amhrt.org/> > to access the following journals:

- *Arteriosclerosis, Thrombosis, and Vascular Biology*
- *Circulation*
- *Circulation Research*
- *Stroke*
- *Hypertension*

#### American Medical Association

< <http://www.ama-assn.org/> > to access the following journals:

- *Journal of the American Medical Association (JAMA)*
- *Archives of Internal Medicine*
- *Archives of Dermatology*
- *Archives of Family Medicine*
- *Archives of Ophthalmology*
- *Archives of Neurology*
- *Archives of General Psychiatry*
- *Archives of Otolaryngology-Head & Neck Surgery*
- *Archives of Pediatrics & Adolescent Medicine*
- *Archives Journal Club—Women's Health*

#### Other Medical Journals

- *British Medical Journal* < <http://www.bmj.com/> >
- *The Lancet* < <http://www.thelancet.com> >
- *Mayo Clinic Proceedings* < <http://www.mayo.edu/publication/proceedings/prologue.htm> >
- *Military Medicine* < <http://www.amsus.org/milmed.html> >
- *Nature* < <http://www.nature.com/> >
- *New England Journal of Medicine* < <http://www.nejm.org> >
- *Postgraduate Medicine* < <http://www.postgradmed.com/journal.htm> >
- *Scientific American* < <http://www.sciam.com> >

## Tri-Service Formulary Selection for Vulvovaginal Candidiasis

In October 1996, the PEC published the pharmacoeconomic model for the treatment of vulvovaginal candidiasis (PEC Update 97-01, 15 October 1996). At that time, clotrimazole 500 mg vaginal tablet was added to the Tri-Service Formulary (TSF) since it represented the most cost-effective therapy for candidiasis. However, this product has been on back order from the manufacturer for at least the last 6 months. Because this product is still unavailable with no anticipated release date (personal communication, Customer Service Dept., Bayer, Inc., March 7, 1997), the PEC has revised the TSF selection for this disease state.

Based on the rank order list of the analysis results, clotrimazole 200 mg ( $2 \times 100$  mg) vaginal tablets daily for 3 days is the preferred regimen (Table). A package with 7 clotrimazole 100 mg vaginal tablets is used for this regimen. Patients must be counseled to insert  $2 \times 100$  mg clotrimazole vaginal tablets daily for 3 days of therapy. The patient will have one vaginal tablet remaining after a course of therapy; this extra tablet should be discarded. Miconazole 2% topical cream should be provided if the patient has vulvar involvement.

The TSF Quick Reference Guide included on page 6 of this Update reflects the addition of clotrimazole 100 mg vaginal tablets and the deletion of clotrimazole 500 mg vaginal tablet from the TSF.

**Table.**—Mean cost-effectiveness (C-E) (cost per clinical cure) after Monte Carlo analysis.\*

Rank after Monte Carlo Analysis	Drug Regimen	Average C-E after Monte Carlo Analysis	95% Confidence Intervals	Rank at Baseline
1	Clotrimazole 500 mg vaginal tab $\times$ 1 day	\$24.52	24.06 - 24.98	1
	Clotrimazole 500 mg vaginal tab kit $\times$ 1 day†	\$26.53	26.05 - 27.01	
2	Clotrimazole 200 mg vaginal tab $\times$ 3 days	\$28.87	28.38 - 29.36	2
3	Fluconazole 150 mg oral tab $\times$ 1 day	\$29.52	29.01 - 30.03	3
4	Clotrimazole 1% vaginal cream $\times$ 7 days	\$30.83	30.34 - 31.32	4
5	Miconazole 2% vaginal cream $\times$ 7 days	\$31.79	31.29 - 32.28	5
6	Clotrimazole 100 mg vaginal tab $\times$ 7 days	\$33.61	33.10 - 34.13	6
7	Miconazole 100 mg vaginal suppository $\times$ 7 days	\$33.70	33.18 - 34.21	7
8	Butoconazole 2% vaginal cream $\times$ 3 days	\$39.66	39.06 - 40.26	8
9	Terconazole 80 mg vaginal suppository $\times$ 3 days	\$40.34	39.73 - 40.94	10
10	Terconazole 0.8% vaginal cream $\times$ 3 days	\$40.55	39.95 - 41.16	9
11	Miconazole 200 mg vaginal suppository $\times$ 3 days kit†	\$41.41	40.79 - 42.02	11
	Miconazole 200 mg vaginal suppository $\times$ 3 days	\$42.12	41.50 - 42.74	
12	Terconazole 0.4% vaginal cream $\times$ 7 days	\$44.52	43.91 - 45.14	13
13	Tioconazole 6.5% vaginal ointment $\times$ 1 day	\$44.78	44.12 - 45.44	12

\* See PEC Update 97-01, 15 October 1996 for the full description of the analysis and results. This table is Table 3 in the full text document.

† Clotrimazole 500 mg vaginal tablet kit contains the vaginal tablet plus a tube of clotrimazole topical cream; miconazole 200 mg vaginal suppository kit contains 3 vaginal suppositories plus a tube of miconazole topical cream.

## Tri-Service Formulary Quick Reference Guide

<p><b>Antimicrobials / Antifungals</b>            *amoxicillin oral suspension and caps            *Bactrim™/Septra® susp and tabs            *dicloxacillin oral            *doxycycline 100 mg caps            *erythromycin oral suspension and tabs or caps            *erythromycin/sulfisoxazole susp            *griseofulvin 125 mg tabs            *isoniazid 300 mg tabs            *metronidazole 250 mg tabs            *nystatin oral suspension            *penicillin VK susp and 250 mg tabs            *rifampin 300 mg caps            *tetracycline 250 mg caps</p> <p><b>Antibiotics-EENT</b>            *Cortisporin® Otic Suspension            *gentamicin ophth. soln. 0.3%            *Neosporin® Ophth. Solution            *sulfacetamide ophth. oint. 10%</p> <p><b>Antivirals</b>            acyclovir 200 mg caps</p> <p><b>Anthelmintics</b>            mebendazole 100 mg chew tabs</p> <p><b>Antiulcer Drugs</b>            *amoxicillin oral            *bismuth subsalicylate 262 mg tabs            *metronidazole 250 mg tabs            *tetracycline 250 mg caps</p> <p><b>GERD Agents</b>            cisapride 20 mg tabs            omeprazole 20 mg caps</p> <p><b>Other GI Agents</b>            *dicyclomine tabs or caps            *Donnatal® tabs            *sulfasalazine 500 mg tabs</p> <p><b>Anti-diarrheals</b>            *loperamide 2 mg tabs or caps</p> <p><b>Genitourinary Agents</b>            *oxybutynin 5 mg tabs            *phenazopyridine 100 mg tabs</p> <p><b>Gout Agents</b>            *allopurinol tabs            *probenecid 500 mg tabs</p> <p><b>Muscle Relaxants</b>            *diazepam 5 mg tabs            *methocarbamol 500 mg tabs</p> <p><b>Oral Corticosteroids</b>            *prednisone 5 &amp; 20 mg tabs            prednisone oral soln 5 mg/5 mL            prednisolone oral soln 15 mg/5 mL</p>	<p><b>Nasal Corticosteroids</b>            *beclomethasone nasal inhaler</p> <p><b>Asthma Agents</b>            *albuterol oral inhaler            flunisolide oral inhaler            triamcinolone oral inhaler            *theophylline liquid 80 mg/15 mL            SloBid™ Gyrocaps 50, 200, 300 mg</p> <p><b>Antihistamines / Decongestants</b>            *Actifed® tabs            *chlorpheniramine 4 mg tabs            *chlorpheniramine syrup            *Dimetapp® Elixir            *Dimetapp® Extentabs            *diphenhydramine caps            *diphenhydramine syrup            *hydroxyzine syrup            *hydroxyzine tabs            *oxymetazoline nasal spray            *pseudoephedrine 30 mg tabs</p> <p><b>Anticonvulsants</b>            †Dilantin® Infatabs 50 mg            †Dilantin® Kapseals 100 mg            †phenobarbital elixir 20 mg/5 mL            *phenobarbital 30 mg tabs            *primidone 250 mg tabs            †Tegretol® 200 mg tabs</p> <p><b>Anticoagulants</b>            warfarin 5 mg tabs</p> <p><b>Diuretics</b>            *furosemide 40 mg tabs            *hydrochlorothiazide tabs            *Maxzide® tabs            *spironolactone 25 mg tabs</p> <p><b>Vasodilators</b>            *isosorbide dinitrate 10 mg tabs            nitroglycerin sublingual tabs</p> <p><b>Lipid Lowering Agents</b>            colestipol powder            *niacin tabs            pravastatin 10 mg, 20 mg, 40 mg tabs</p> <p><b>Hypotensive / Cardiac Drugs</b>            *atenolol tabs            *clonidine tabs            †Lanoxin® 0.25 mg tabs            lisinopril tabs            *propranolol 10 &amp; 40 mg tabs            *quinidine gluconate 324 mg tabs            *quinidine sulfate tabs            terazosin tabs            *verapamil long-acting tabs</p> <p><b>Electrolyte Replacement</b>            *potassium chloride slow release tabs or caps</p>	<p><b>Diabetic Agents</b>            *human insulin, regular &amp; NPH</p> <p><b>NSAIDs / Analgesics</b>            *acetaminophen drops, elixir, and 325 mg tabs            *aspirin, enteric-coated 325 mg tabs            *ibuprofen susp and 400 mg tabs            *indomethacin 25 mg caps            *Tylenol #3® tabs</p> <p><b>Migraine Agents</b>            *Cafergot® tabs            *Fiorinal® tabs            *Midrin® caps</p> <p><b>Attention Deficit / Narcolepsy Agents</b>            *methylphenidate 10 mg tabs            *methylphenidate sustained release 20 mg tabs</p> <p><b>Contraceptives</b>            LoOvral®            *Norinyl 1+50®, Ortho-Novum 1/50®            *Ortho-Novum 1/35®, Norinyl 1+35®            Ortho-Novum 7/7/7®            Ovral®            Triphasil®/Tri-Levlen®</p> <p><b>Estrogens / Progestins</b>            conjugated estrogens 0.625 mg tabs            conjugated estrogen vaginal cream            *medroxyprogesterone 10 mg tabs</p> <p><b>Thyroid / Antithyroid Agents</b>            *propylthiouracil 50 mg tabs            †Synthroid® 100 mcg (0.1 mg) tabs</p> <p><b>Topical Agents</b>            *bacitracin ointment            *hydrocortisone 1% cream            *miconazole 2% topical cream            Sebutone® shampoo            *Selsun® shampoo</p> <p><b>Vaginal Antifungal Agents</b>            clotrimazole 100 mg vaginal tab</p> <p><b>Vitamins &amp; Minerals</b>            *ferrous sulfate concentrated soln. 125 mg/mL            *ferrous sulfate 325 mg tabs            *pyridoxine 50 mg tabs</p> <p><b>Miotics</b>            *pilocarpine ophth. solution</p> <p><b>Miscellaneous</b>            insect sting kit            InspirEase® spacer</p> <p><b>* generic products are available</b>  <b>† sole source item</b></p>
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**Brand names are included for example only and are not meant to imply the recommendation of a specific product except for those products designated as sole source items by the Pharmacoeconomic Center.**

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